DEFINING THE DIFFERENCE: WHAT MAKES BIOLOGICS UNIQUE

Biologics differ from chemically derived drugs in ways that affect their cost, production, administration, and clinical efficacy. Here's a look at the most important differences and their implications.

BY THOMAS MORROW, MD

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"The difference between the almost right word and the right word is really a large matter — it is the difference between the lightning bug and the lightning." Mark Twain's observation on the importance of three little letters applies to the differences between biologically and chemically derived medications. This time, though, the three letters are *DNA*.

Protein-based biologics and devices are used to treat everything from wrinkles to rattlesnake bites, and range from natural protein sutures to fibrinogen coagulant factors. Biotechnological applications in healthcare encompass prophylactic agents, *in vivo* diagnostic tools, and therapeutic products. Biotechnology provides imaging agents and molecular diagnostic tests for detecting a wide range of health problems, from excessive LDL levels to drug-resistant HIV strains.

Advances in this field are rapidly turning Western medicine inside out. Rather than start with a disease and search for its origin, biotech medicine begins with the detection of a genetic variation and relies on therapies that manipulate it. Carrying the concept further, it holds promise for predicting health status and acting accordingly — the very notion of prevention on which managed care was founded.

None of this is inexpensive, however, thus posing profound issues of resource use and appropriate selection of patients. Purchasing and using biologic agents effectively, then, necessitates an appreciation of their enigmatic activity and structure, the specificity of their action, and the ways in which they differ from traditional therapeutic agents.

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OLD IDEA, NEW ADAPTATION

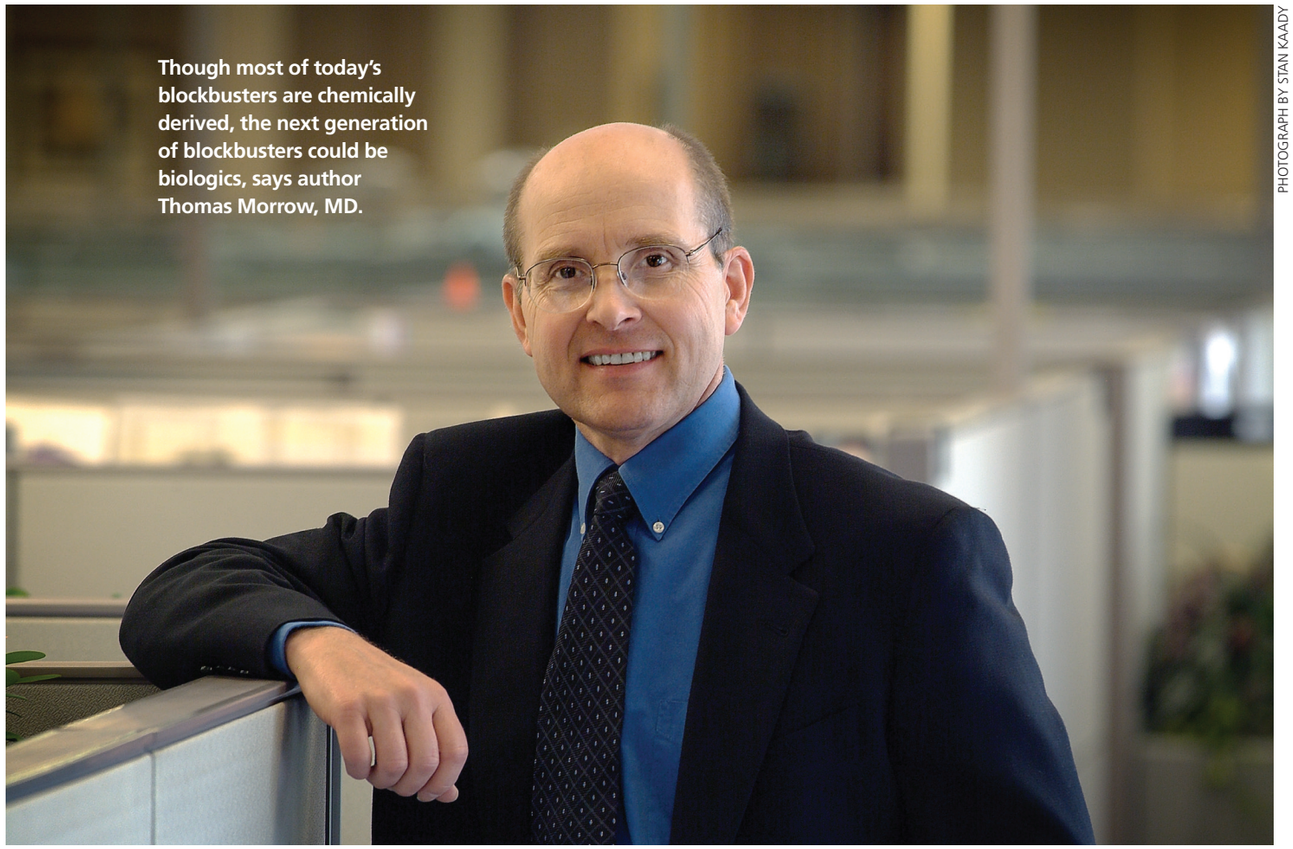
Biologics are not new; development of human growth hormone, insulin, and red-blood cell stimulating agents occurred decades ago, but the targets have increased exponentially with new genetic information and new understanding of subcellular cascades and disease processes. Scientific fields used in developing biologics include genomics and proteomics, as well as microarray, cell culture, and monoclonal antibody technologies.

Increasing knowledge of genetics and cell processes leads to potential new biologic (and drug) targets at each step in the protein-production process. This leads to new therapies, which in turn lead to new understanding of diseases.

Biologics have identified new targets for treating anemia, cystic fibrosis, growth deficiency, diabetes, hemophilia, hepatitis, genital warts, transplant rejection, and cancers. Biologics predict genetic propensity to diseases such as Parkinson's disease. Nondrug biologics include cultured tissues and immune system suppressants for transplantation and growth factors for tissue reconstitution to treat conditions such as diabetic foot ulcers.

As with small-molecule drugs, research and development of biologics is expensive and risky, often ending in failure. While pharmaceutical companies target the most common diseases and conditions, biotech has tended to target more difficult-to-treat populations that would be too small for pharmaceutical companies to be able to recoup drug-development costs. Yet, newer biologics also are targeting widespread diseases, with profound implications: a drug that costs $20,000 per year that is useful for 1 person in 100,000 has much less effect on a health plan's cost structure than a $5,000-per-year drug that is useful for 1 in 100 people.

Many of the next blockbusters may well be biologics. Two antidiabetic drugs, Symlin (pramlintide acetate) and Exenatide (synthetic exendin-4), meet the definition of a biologic. So do the monoclonal antibodies and TNF inhibitors, as well as angiogenesis inhibitors — such as the newly released Avastin (bevacizumab) and Erbitux (cetuximab).



Though most of today's blockbusters are chemically derived, the next generation of blockbusters could be biologics, says author Thomas Morrow, MD.

PHOTOGRAPH BY STAN KAADY

ORGANIC ORIGINS

Currently, there is no simple way to define all the drugs that are reported to be biologics. There are multiple factions that wish to define biologics in various ways. Some would apply a strict definition of biologics dictating that these products share two critical traits that distinguish their physical makeup from chemically derived drugs: only living systems can produce them, and biologics are relatively large molecules, with an inherently heterogeneous structure that can contain hundreds of amino acids.

Some groups would expand the definition of biologics to include any substance composed of organic molecules, no matter how small. Still others feel that any biologically derived product can be called a biologic, and still more think that any complex molecule — no matter how it is manufactured — should be in this class. Others would include substances that are created in other organisms but are not highly complex, such as the estrogen hormones extracted from pregnant mare urine (Premarin).

No matter what definition is used, it is likely to need to be modified as new products are brought to market. With a few exceptions, this article will use the definition that biologics are created by either a microorganism or mamallian cell and are large complex molecules, most of which are proteins or polypeptides.

Chemical drugs are often more pure and better characterized by current analytical technology than biologics. A biologic agent's activity may be affected by the cell system in

which it is produced, the fermentation media, or operating conditions.

The production process of chemical drugs is relatively well defined, which allows these drugs to be produced in uniform large quantities. Biologics, however, have a complex production process that tends to yield small quantities. It is difficult to scale up biologics from laboratory quantities used for early analysis and preclinical testing to larger-scale batches and maintain product purity and batch-to-batch equivalence.

The use of living organisms to produce therapeutic extracts is not new. What is new is manipulation of these organisms' genetics to produce specific therapeutics.

Biologics are often extremely sensitive to physical conditions (temperature, shear forces, chemical phase, and light) and enzymatic action. They usually require complex bioassays for batch release and stability assessment, rather than chemical tests for identity and purity.

HOW THEY WORK

The therapeutic target of a biologic is always a gene or a protein. The fact that genetic information is decoded similarly among all cells, regardless of species, allows humans to study gene function in worms or zebra fish.

Recombinant DNA, an important process for producing biologics, requires isolating the DNA from human cells and potentially modifying that DNA segment, inserting it into bacteria or a mammalian cell, and getting that organism or cell to express it. Several steps are involved in the development process: locating genes that code for proteins, cloning genes, reproducing the proteins associated with the genes, determining the role of the proteins in the disease process, and then developing a potential therapy.

All new proteins that are identified undergo a series of cell-based assays providing information on how a specific protein changes a biological process. Bioassays to determine potency use biological indicators of living organisms or tissues. These can include cell-based tissue cultures, microarray expression technology, knockout animal models, transgenic animal models, and antisense or antibody technology (e.g., diagnostic antibody characterization).

There is a greater potential for immune reactions to biologics than to chemical drugs. The molecules in chemical drugs are too small to be considered immunogenic and generally are not recognized by the immune system as "invaders." With biologics, depending on the drug, the human immune system can quickly identify the molecule and then mount an immune response to clear away a large molecule that it considers a foreign substance. This can destroy — or in rare cases, enhance — the activity of the biopharmaceutical.

Almost all biologics can induce the production of antibodies, though most antibodies have benign clinical consequences. The antibodies may be caused by tiny contaminant fragments, contact with the patient's serum, or post-dose enzymatic cascades.

COMPLEX MANUFACTURE

The fragility of biological macromolecules and the sensitivity of the living cells that produce biologics impart complex manufacturing requirements for fermentation, aseptic processing, storage, and testing. Although the active ingredient of a chemical pharmaceutical is usually a unique molecule subject to well-established analytical tests, for biologics, the active component often is a portion of a large macromolecule. That macromolecule is in turn a modification of the original protein or polypeptide and other biological substances that may not be clearly characterized. Protein and polypeptide products can contain variable complexes, meaning that they have variable numbers of identical components in the molecules. Also, biologics may have differences in their surface sugars (glycosylation) or folding patterns, depending on how they are produced. With biologics, there is also potential for microbiological contamination of the starting materials.

Because biologics are often heterogeneous in the molecules and/or polypeptides present, they have an impurity profile that depends on — and can vary with — the processes used to make and test each batch. With biologics, the protein mix must be defined, and the active agent and supporting agents must be characterized. In other words, the product does not need to be homogeneous if the biologic acts via a molecular group. Blood, for instance, is a biologic (according to U.S. Food and Drug Administration

Selected categories of biologic agent structure
Hormone (growth hormone, parathyroid hormone, insulin): A substance, usually a peptide or steroid, produced by one tissue and conveyed by the bloodstream to another to effect physiological activity, such as growth or metabolism.
Interferons: Proteins that are normally produced by cells in response to viral infection and other stimuli.
Interleukins: A large group of cytokine proteins. Most are involved in directing other immune cells to divide and differentiate.
Growth factor: A substance such as a vitamin B12 or an interleukin that promotes growth, especially cellular growth.
Monoclonal antibodies (MAbs): A single species of immunoglobulin molecules produced by culturing a single clone of a hybridoma cell. MAbs recognize only one chemical structure, i.e., they are directed against a single epitope of the antigenic substance used to raise the antibody.
Polypeptides: Peptides containing ten or more amino acids. Typically, a peptide consists of fewer than 50 amino acids, while a protein has more than 50 amino acids.
Proteins: Naturally occurring and synthetic polypeptides having molecular weights greater than about 10,000 (the limit is not precise).
Vaccine: An agent containing antigens produced from killed, attenuated or live pathogenic microorganisms, synthetic peptides, or by recombinant organisms. Used for stimulating the immune system of the recipient to produce specific antibodies providing active immunity and/or passive immunity in the progeny.
SOURCES: International Union of Pure and Applied Chemistry *Compendium of Chemical Terminology, 2nd edition*, 1997; Cambridge Healthcare Institute «www.genomicglossaries.com»; National Multiple Sclerosis Society Sourcebook «http://www.nationalmssociety.org/Sourcebook.asp».

classification) that is not composed of a single uniform molecule.

This is not to suggest that there is a lack of quality-control measures for biologic manufacture; actually, just the opposite is true. A typical manufacturing process for a chemical drug might contain 40 to 50 critical tests. The process for a biologic might contain 250 or more. Biologic production uses specialized processes that do not always resemble facilities, machinery, or equipment used to produce chemical drugs. Construction and validation of new facilities is disproportionately expensive and also time consuming. This helps explain the global shortage of biomanufacturing capacity and the cost differential between biologic and chemical drugs.

Changing a manufacturing process typically presents fewer challenges with chemical drugs than it would with biologics. Chemical drug batches are released according to specifications for the drug substance and the final product, without the extensive characterization and critical testing required of biologics.

DOSAGE AND DISTRIBUTION

Biologics can cost thousands of dollars monthly and require special handling, as they are often less stable than chemically derived drugs and require controlled temperature and light, as well as protection from jostling when in liquid form. For example, many large proteins cannot be shaken to reconstitute, as shaking can destroy the protein structure.

Biologics are medications targeted to specific genotypes or protein receptors. They are most commonly stored, handled, and delivered by specialty pharmacies, distributors that specialize in administering complex-molecule products for small populations and have specialized handling and processing and mailing processes in place to accommodate these complex medications. In many ways, biologics are considered designer drugs that are targeted for patients with uncommon diseases or for genetic subclasses of patients who have widely prevalent diseases.

For some very rare disorders, such as Gaucher's disease, the number of patients in the United States might not exceed 1,000. The high cost of developing and marketing a product, combined with a small target population translates into a considerable per-patient cost. Often, specialized clinics treat patients and/or administer these drugs.

Dosage forms of chemical drugs are highly variable, and concentrations usually are easy to determine. Yet, because biologic molecules are too large to be taken orally without being destroyed before passing

through the intestine into the blood stream, they usually are injected or infused. Also, potency is more difficult to quantify for biologic agents, and monitoring is a key component of early therapy.

New modes of administration, such as via food that is directly or indirectly transgenic, are being studied. An example of the latter is goat's milk that produces an antimalarial compound. Transdermally administered vaccines also are under investigation.

REGULATORY ISSUES

The FDA precisely defines biologic therapies and devices for regulatory purposes. A product's intended use may dictate its classification — e.g., an *in vitro* diagnostic kit may fit a classic definition of a medical device but may still be defined as a biologic, as it is used to test and release a licensed biological product such as blood. A similar kit used to test blood samples for diagnosing a disease like rubella, or for monitoring a disease's progress, may fall under medical device regulations due to its usage in diagnosing human disease.

With biologic products, the manufacturing process is part of the patent and is subject to regulatory approval. Process changes trigger the need for new clinical trials, yielding greater development costs. Partly to remedy this, the FDA's Center for Biologics Evaluation and Research (CBER) has developed draft guidelines for a postapproval comparability protocol allowing companies to combine several manufacturing changes into a single abbreviated postapproval application when they change their process. Companies are not required to duplicate clinical studies after a drug manufacturing change, if they can show that it is bioequivalent and causes no new adverse reactions.

Many biologic products — some vaccines, gene therapies, antitoxins, blood, and some *in vitro* diagnostics, to name a few — are approved by CBER. Remaining categories, including monoclonal antibodies, growth factors, enzymes, immunomodulators, and thrombolytics, are the domain of the Center for Drug Evaluation and Research (CDER). Generic (more accurately, follow-on) biologics are not legal in the United States, and no regulatory pathway exists for their approval.

With pretreatment genetic testing, large clinical studies may become obsolete. Conventional clinical trials involve extrapolation to larger populations to predict medical outcomes in much larger populations; to date, however, biologics have not been aimed at large heterogeneous populations, so conducting large trials is wasteful. Also, the risk/benefit ratio of a drug for an otherwise fatal disease is skewed toward efficacy versus safety. This is not true of a conventional drug for a chronic condition, such as hypertension — for which there are many relatively safe treatment options.

WEIGHING COSTS, VALUE

Biologics, though much more expensive than chemical entities, are generally considered by health care providers and payers to be worth their cost — as long as the appropriate patients receive them and achieve the desired clinical outcomes. Patients for whom biologics are a good value include those who have failed on conventional therapies or for whom no other options exist. For some drugs, assays assist in patient selection. The cost of DNA-based tests and the expense of educating clinicians on their use must be factored into the net value.

EXCITING FUTURE

Looking ahead, several promising technological advances are in various stages of readiness, each with deep implications.

RNA interference allows better characterization of the function of a specific gene or DNA fragment. Antisense molecules (small pieces of DNA or RNA) prevent production of the protein encoded in that blocked DNA or RNA, effectively "knocking out" the gene. The knockout procedure also is used to determine the function of a specific gene in laboratory animals. This knowledge then can be extrapolated to corresponding human genes. The physical manifestation of a trait or disease is usually the culmination of many steps involving a protein-to-protein chain reaction, starting from gene expression and going through a cascade of small events in which a molecule is changed by enzymes and then handed off to other enzymes for further changes.

Scientists are studying the relationship among genes, traits, and proteins by blocking gene expression and characterizing the resulting biological or visible changes. The knowledge gained will help in targeting future therapies. Replacement gene therapy, which targets diseases such as hemophilia caused by the lack of a protein, is one direction of research.

Science is rapidly unlocking the secrets of human DNA. Healthcare is catching up with it. **BH**